

ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Diseases

Section Editor: Stephen B. Hanauer, MD

Utility of TPMT Testing and Metabolite Monitoring in the Management of IBD

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G&H Can you explain the metabolic pathways that affect the bioavailability of orally administered immunosuppressive agents?

MO Initially, azathioprine (AZA) is converted to 6-mercaptopurine (6-MP) and 6-MP is metabolized by three different enzymes (Figure 1). The primary metabolic action is via the enzyme xanthine oxidase (XO), which metabolizes 6-MP to its inactive form, 6-thiouric acid (6-TU). The oral bioavailability of active 6-MP is only in the range of 5–37% due to this metabolism by XO. The two remaining enzymes, thiopurine methyltransferase (TPMT) and hypoxanthine phosphoribosyltransferase (HPRT), which we focus on for therapeutic purposes, are actually minor contributors to 6-MP metabolism. The HPRT pathway leads to the active therapeutic metabolites of 6-MP, the 6-thioguanine nucleotides (6-TGN), which are also thought to be responsible for its associated myelotoxicity and potentially for its hepatotoxicity as well. TPMT converts 6-MP to other active metabolites, the 6-methylmercaptopurine ribonucleotides (6-MMPR), which, although not biologically active in terms of efficacy, may play a role in hepatotoxicity (but this is controversial).

G&H Can you describe the difference between TPMT testing and metabolite monitoring, in terms of what they measure and how they are utilized in the administration of immunosuppressive therapies?

MO The utility of testing for the metabolism of TPMT was illustrated by a study conducted at the Mayo Clinic in 1980, where 298 healthy adults in Olmstead County,

Minnesota and surrounding areas were shown to fall into three widely varying categories with regard to TPMT activity. Roughly 89% of patients fell into the category of normal metabolizers, with a high level of TPMT activity. Approximately 11% fell into the category of intermediate metabolizers, with a lesser level of activity. One subject out of the 298 studied, or 0.3%, had very low activity. More recently, rare patients have been found who have no TPMT activity. These variations in TPMT metabolism cause corollary differences in the way immunosuppressive drugs are absorbed, potentially affecting the levels of active drug shunted to the HPRT pathway. For patients with low or no TPMT activity, standard doses of AZA and 6-MP can cause a potentially adverse reaction, leading to dangerously low white blood cell (WBC) counts, neutropenia, and even sepsis and death.

Thus, when we test for TPMT activity, one reason we do so is as a safety measure. The other reason is that knowing the rate of TPMT metabolism allows us to commence therapy with immunosuppressives at the target dose (2–3 mg/kg/day of AZA and 1.5 mg/kg/day of 6-MP for normal metabolizers and half of those doses for intermediate metabolizers), rather than stepping up slowly and monitoring for adverse reactions. Starting the patient at target dose allows us to achieve efficacy more

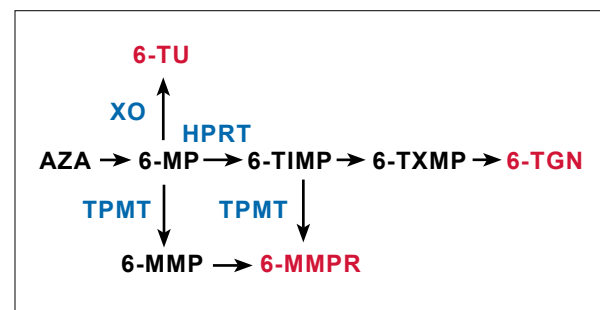


Figure 1. Model of thiopurine metabolism.

AZA=azathioprine; 6-MP=6-mercaptopurine; XO=xanthine oxidase; 6-TU=6-thiouric acid; TPMT=thiopurine methyltransferase; HPRT=hypoxanthine phosphoribosyltransferase; 6-TGN=6-thioguanine nucleotides; 6-MMPR=6-methylmercaptopurine ribonucleotides.

quickly and also allows us to stop the drug more quickly in patients for whom it is not working. For patients with little or no activity of the enzyme, we avoid thiopurines altogether and consider alternate therapies.

The utility of metabolite monitoring, where levels of 6-TGN and 6-MMPR are checked, is more controversial, as it has not been shown definitively and uniformly to affect patient outcomes. Our center performed a meta-analysis of studies in which these metabolite levels were measured and found that patients who have 6-TGN levels above 230–260 pmol/ 8×10^8 red blood cells (RBCs) had a higher likelihood of response to thiopurines. Therefore, one way to utilize metabolite level information is to dose-adjust to target 6-TGN levels in this range in order to achieve response.

Another way to utilize the information is to consider the ratio of 6-MMPR to 6-TGN. A study by Dubinsky and associates, published in *Gastroenterology* in 2002, looked at metabolite-guided thiopurine dose escalation among 51 initial nonresponders to thiopurines. The group that eventually achieved response had ratios of 6-MMPR to 6-TGN of 2.5–9.1, likely due to shunting to the HPRT pathway, whereas nonresponders tended to have higher ratios of 6-MMPR to 6-TGN of 18–66, likely due to shunting to the TPMT pathway. In clinical practice, we generally use a cutoff for the 6-MMPR to 6-TGN ratio of 20 and recommend considering dose escalation for patients with a ratio of less than 20 and changing to a different agent for patients with a ratio greater than 20 in order to optimize therapy. One other point that deserves mention is that patients with low levels of both 6-MMPR and 6-TGN are likely underdosed, malabsorbing the drug, or most often noncompliant. In this way, measuring metabolite levels can help physicians ascertain that their patients are in fact taking their prescribed medication.

G&H What evidence is available to show the effect of utilizing metabolite monitoring to adjust dosage on long-term outcomes?

MO One small, prospective, controlled study, by Reinshagen and associates, published in 2007, started all patients on AZA at 2.5 mg/kg/day and randomized them to having dose adjustments based on metabolites versus having no such dose adjustments based on metabolite levels and found that the rates of remission in the two groups were nearly identical during the 24 weeks of follow-up. Thus, perhaps the most important clinical decision is to start patients at their target dose of thiopurines. The results of a larger randomized study of dose adjustment by level, conducted by Hanauer and colleagues, should be available shortly. The information

from this study will be important in helping to decide the overall utility of metabolite monitoring. However, even if this study shows similar clinical outcomes, there still may be individual cases in which metabolite monitoring may have value, most notably those who have shunting to the TPMT or HPRT pathway and those who are noncompliant.

G&H What cost-effectiveness data are available in connection with these tests?

MO There are at least two published cost-effectiveness analyses. The first was published by Winter and associates in 2004, focusing on safety advantages when utilizing TPMT testing to decrease potential leukopenia. They assumed a 3.2% risk of leukopenia in the overall patient population (100% risk among homozygous recessive patients who were nonmetabolizers of the drug, 6.4% in intermediate heterozygotes, and 2.5% in wild-type patients, acknowledging that even if TPMT levels are normal, myelosuppression is still possible). They also assumed a 32% risk of myelosuppression due to TPMT deficiency and a 0.1% risk of death from leukopenia overall (but 3% among leukopenics). Their analysis found that the cost-per-life-year saved by utilizing TPMT testing was £347 for a 30-year-old patient and £817 for a 60-year-old patient and that, therefore, TPMT testing was cost-effective from a safety standpoint.

Another study by Dubinsky and colleagues looked at cost-effectiveness from an efficacy standpoint and considered TPMT testing and/or metabolite monitoring. In this model, patients were started at low doses of AZA in an effort to reflect community practice, where physicians often start their patients at a low dose and ramp them up slowly. The investigators compared TPMT testing, metabolite monitoring, or a combination of both, to routine community care of doing neither. For patients undergoing metabolite monitoring, dose increases could be made at Week 4 and every 8 weeks thereafter, whereas those who had TPMT testing only could dose escalate every 3 months; patients receiving community care could only escalate once at 3 months. The authors assumed that, of the patients who did not respond to thiopurines, 75% would receive infliximab and 25% would undergo surgery. Creating their model this way, they calculated that each monitoring strategy was not only cheaper, but also more effective in terms of time to response, than the community care strategy.

Regardless of these findings, it is important to consider the expense of these assays, particularly for uninsured patients who need to pay out of pocket. Even for insured patients, policies may not cover TPMT and metabolite monitoring at regular intervals.

G&H What will need to take place in order for insurers to cover the cost of these tests?

MO Insurers may be looking for clear differences in clinical efficacy associated with the use of TPMT testing and metabolite monitoring. If these findings are established, it would be difficult for insurers to argue against paying for the tests. The cost-effectiveness data described above have been available for several years but do not seem to have made much impact on insurance coverage.

G&H Can you describe recent research into the use of allopurinol as an immunosuppressive co-therapy? How might this practice change the role of metabolite monitoring?

MO Sparrow and associates recently conducted a small study of allopurinol as an adjunct to thiopurines in 20 patients who were initial nonresponders to thiopurines but whose ratios of 6-MMPR to 6-TGN suggested shunting to the TPMT pathway. The authors hypothesized that because allopurinol is such a potent inhibitor of XO, the primary enzyme that metabolizes 6-MP, more 6-MP substrate would be available for the other two pathways and that 6-TGN production would increase, with a corresponding increase in efficacy. For this same reason, the investigators decreased the thiopurine dose by 25–50% in an attempt to prevent dangerous levels of neutropenia. This study found that after 3 months of allopurinol therapy, even with much decreased doses of thiopurines, they could recapture response in some patients via allopurinol co-administration as well as decrease the need for corticosteroids. Interestingly, the investigators also found that, whereas 6-TGN levels went up, 6-MMPR levels went down when allopurinol was administered, indicating some additional mechanism beyond inhibition of XO.

Although this strategy requires a commitment from both the physician and the patient to careful complete blood count (CBC) monitoring, it may be useful in select patients with a 6-MMPR to 6-TGN ratio indicative of shunting to the TPMT pathway. In these cases, metabolite monitoring would be needed to establish that ratio and to monitor the effect of allopurinol on subsequent 6-TGN levels.

G&H What other issues need to be resolved in order to optimize the use of TPMT testing and metabolite monitoring?

MO With respect to TPMT testing, the primary limitation, aside from cost, is that following patients' CBCs, particularly in the first weeks of therapy, is more impor-

tant. For instance, two studies published in *Gastroenterology* in 2000, one by Dubinsky and colleagues and the other by Colombel and associates, found that only 8% and 27%, respectively, of patients with leukopenia had mutations in the TPMT genotype. Thus, TPMT testing should never supplant strict regular monitoring of CBCs. A recent study by Lewis and associates at the University of Pennsylvania and Kaiser Permanente reported that thiopurine-associated leukopenia occurs most often in the first 8 weeks of therapy. For this reason, physicians need to be hypervigilant about following CBCs in the initial period. However, TPMT testing is useful to identify patients with mutant alleles who may need lower dosing or consideration of alternate therapy and to start patients at the target dose, which may lead to faster response or knowing sooner that these drugs will not work so that patients may stop treatment quickly to minimize the risk of toxicity.

With respect to metabolite monitoring, its main limitations, aside from cost, are that it is imperfect in its predictive abilities and that there is a lack of prospective data on its clinical impact. In our meta-analysis of 6-TGN levels, only 62% of patients who were above the established therapeutic threshold were in remission. Among those patients not achieving threshold levels, 36% were in remission. Thus, using 6-TGN levels as a clinical guide is potentially useful but far from perfect. Until the large randomized study by Hanauer and colleagues is published, we will not know the true clinical impact of thiopurine dose adjustment according to metabolite levels.

Unfortunately, there is currently no superior alternative to metabolite monitoring. Two factors that have been studied are mean corpuscular volume (MCV) and CBC. A study conducted at the Mayo Clinic, by Thomas and associates, observed very low correlations between either MCV or change in MCV and 6-TGN levels. With respect to CBC, although one early study by Colonna and Korelitz suggested that induction of leukopenia was associated with response to thiopurines, at least 4 subsequent studies have refuted this strategy. In addition, inducing leukopenia may be dangerous to patients.

Until all of these issues are resolved and we have definitive data regarding the effect of these tests on long-term outcomes, it is doubtful that they will be widely adopted in the management of our inflammatory bowel disease patients.

Suggested Reading

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